A Convenient Procedure for the Quantitative Conversion of Reactive Alcohols and Olefins into the Corresponding Chlorides

HERBERT C. BROWN AND MIN-HON REI

Richard B. Wetherill Laboratory, Purdue University, Lafayette, Indiana

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The hydrogenator previously described, which generates hydrogen automatically from sodium borohydride to achieve the quantitative hydrogenation of unsaturated compounds, has been adapted to the hydrochlorination of reactive alcohols and olefins. In this procedure hydrogen chloride is generated automatically as required to react with the alcohol or olefin, and the generation ceases when the reaction is complete. In this manner it is possible both to follow the rate of utilization of the hydrogen chloride and to convert the alcohol or olefin essentially quantitatively into product without excessive contact with the hydrochlorination reagent.

Reactive alcohols, such as *t*-butyl alcohol, are readily converted into tertiary chlorides by being shaken at room temperature with excess concentrated hydrochloric acid.[1,2] Alternatively, anhydrous hydrogen chloride may be passed into the alcohol until saturation has been achieved.[3]

In the course of our investigations dealing with the nature of the intermediate formed in the solvolysis of bicyclic derivatives,[4,5] we encountered difficulties in applying these simple procedures to relatively labile bicyclic structures. Excess treatment of the alcohols with the reagent led to the formation of appreciable quantities of undesired by-products. On the other hand, inadequate treatment led to the formation of mixtures of the alcohol and chloride which proved exceedingly difficult to separate. Consequently, we were led to explore the possibility of developing a simple procedure which would permit us to follow the uptake of hydrogen chloride quantitatively, so that the reaction could be halted as soon as all of the alcohol had been converted into the chloride, thereby avoiding either the incomplete conversion or the too exhaustive treatment that had plagued our attempts to utilize the older procedures.

Recently, a simple, but highly effective, apparatus was described for the automatic generation of hydrogen as required for the hydrogenation of unsaturated compounds.[6,7] It appeared that the same apparatus and principle might be adapted to the hydrochlorination of reactive alcohols and olefins. Accordingly, we undertook to study this possibility. *Indeed, we discovered that we could convert many of the bicyclic alcohols and certain reactive olefins essentially quantitatively into the corresponding chlorides at 0° in a reaction time of approximately 100 sec.* Consequently, the procedure not only solved our immediate problem, but it opened up the possibility of reexamining the hydrochlorination of many reactive terpenes where the precise nature of the initial hydrochlorination product may be in doubt.

Procedure

We utilized the commercial model of the preparative hydrogenator.[7] However, in order to avoid possible corrosion of the hypodermic needle of the buret in the preparative unit, we substituted the glass-tipped buret and the corresponding valve of the analytical unit for these two items of the preparative unit. In this way the concentrated hydrochloric acid in the buret comes in contact only with glass and the mercury in the valve before it reacts with the concentrated sulfuric acid in the generator to produce anhydrous hydrogen chloride. The complete assembly is shown in Figure 1.

The following procedure will convert from 10 to 100 mmoles of alcohol or olefin into the chloride. However, it can readily be modified to handle either smaller or larger quantities.

Approximately 200 ml of concentrated sulfuric acid is placed in a 500-ml modified erlenmeyer flask, serving as the generator G. A Teflon-coated magnetic stirring bar is introduced. (It is important that the sulfuric acid be efficiently stirred to effect thorough mixing of the less dense hydrochloric acid phase with the sulfuric acid.) The slight curvature of the flask bottom and the Teflon collar on the stirring bar are not essential for the present application, but they greatly facilitate smooth, efficient stirring of the contents.

The apparatus is assembled so that it is gas tight. In the buret B is placed an adequate amount of concentrated hydrochloric acid. The height of the liquid column must be controlled so that it is supported by the column of mercury in the valve V.

By maens of a small rubber bulb attached to the top of the buret, pressure was supplied to force 3 to 4 ml of concentrated hydrochloric acid through the mercury seal to generate sufficient hydrogen chloride to flush the system. (The amount was selected to provide a volume of hydrogen chloride that was approximately twice the free volume of the system.)

The reaction flask R, usually a 125-ml modified flask, for the usual scale of the preparations, was commonly immersed in an ice bath to provide a convenient reaction temperature. However, in many cases it proved quite satisfactory to carry the reaction out at room temperature, and in some cases quite low temperatures were used.

The reaction is initiated by injecting, by means of a hypodermic syringe, through the introductory port P, 10 to 100 mmoles of the alcohol or olefin, neat, or as a concentrated solution in *n*-pentane, methylene chloride, or carbon tetrachloride. Reaction begins immediately. (It is important that the contents of the reaction flask be stirred vigorously by the usual

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(1) J. F. Norris and A. W. Olmsted, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p 144.

(2) H. C. Brown and R. S. Fletcher, *J. Am. Chem. Soc.*, **71**, 1845 (1949).

(3) H. C. Brown and R. B. Kornblum, *ibid.*, **76**, 4510 (1954).

(4) H. C. Brown and F. J. Chloupek, *ibid.*, **85**, 2322 (1963).

(5) H. C. Brown, F. J. Chloupek, and M.-H. Rei, *ibid.*, **86**, 1246 (1964).

(6) C. A. Brown and H. C. Brown, *ibid.*, **84**, 2829 (1962).

(7) Commercial models of these automatic hydrogenators, both preparative and analytical, are currently available from the Delmar Scientific Laboratories, Inc., Maywood, Ill. 60154.

Teflon-coated bar and magnetic stirrer.) As soon as the pressure drops 10 to 20 mm below atmospheric, concentrated hydrochloric acid is drawn through the mercury seal in the valve V and it then reacts with the magnetically stirred sulfuric acid to generate hydrogen chloride to restore the pressure. The reaction proceeds automatically until absorption of hydrogen chloride ceases, as shown by the behavior of the mercury in the bubbler, or the constancy of the quantity of hydrochloric acid remaining in the buret.

Experiments revealed that under the operating conditions each milliliter of the concentrated hydrochloric acid generated 11.0 ± 0.1 mmoles of hydrogen chloride. In the case of olefins, such as α-methylstyrene, 1 mole of hydrogen chloride was taken up for each mole of olefin. However, in the case of the alcohols, additional hydrogen chloride was utilized to saturate the water produced in the reaction. At 25° each mole of alcohol utilized 1.29 moles of hydrogen chloride, at 0° the corresponding figure was 1.35 moles.

In the case of liquid chlorides, prepared neat from the corresponding alcohols, it was adequate to remove with the aid of a capillary tube the small lower phase of water saturated with hydrogen chloride. After a brief aspiration to remove traces of dissolved hydrogen chloride, the organic phase appeared to be essentially pure tertiary chloride by all of the usual tests. In cases where solvents were employed, it was removed under vacuum to recover the chloride, or the solution was cooled to low temperatures to precipitate the solid chloride.

Results and Discussion

The three aliphatic alcohols, *t*-butyl alcohol, *t*-amyl alcohol, and triethylcarbinol were each injected neat into the reaction flask, maintaining a slow constant rate of stirring in the reaction flask. Under these conditions the reaction required 75, 15, and 7.5 min, respectively, to proceed to completion. The relative magnitudes of the reaction times correspond to the relative ease of formation of the three carbonium ions, as measured by the rates of solvolysis at 25° in 80% aqueous ethanol: 0.033, 0.055, and 0.099 hr^{-1}, respectively.[2,8]

The time required for reaction is a function of the efficiency of stirring in the reaction flask. Thus, by using more vigorous agitation, the time required to convert *t*-amyl alcohol to its chloride was reduced from 15 to 1.3 min. It is probable that the apparatus could be developed into a satisfactory procedure for determining the rate of reaction of such alcohols with hydrogen chloride, but this will require vigorous agitation of the contents of the reaction flask adequate to avoid diffusion control of the observed rate. Since this was not a part of our current objective, we did not attempt to develop such a procedure.

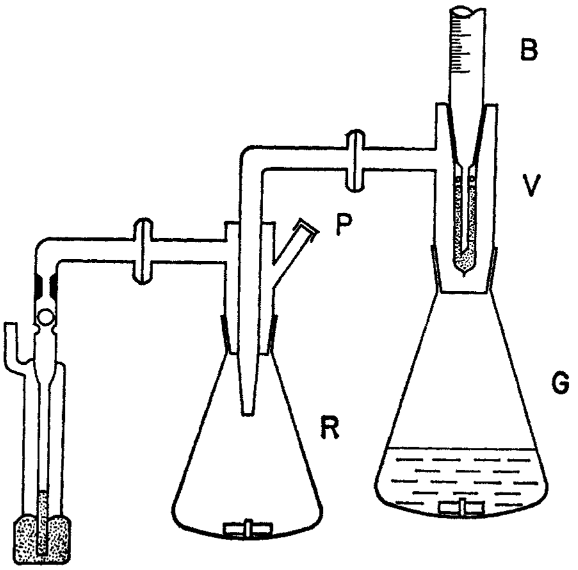

Figure 1.—Apparatus used for the automatic hydrochlorination of alcohols and olefins.

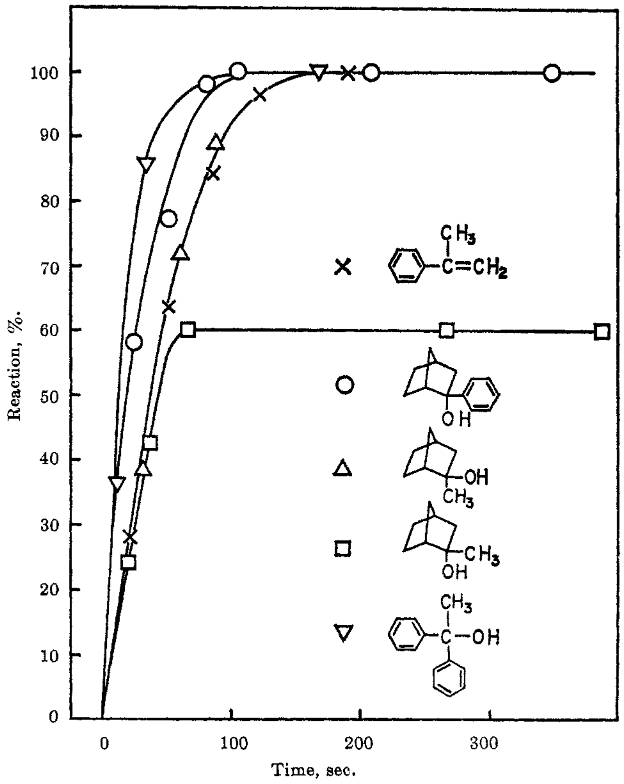

Figure 2.—Hydrochlorination of various alcohols and olefins at 0°.

Perhaps the most unexpected result of our study was the observation that many of the more reactive alcohols, including the bicyclic alcohols of immediate concern to our studies, underwent conversion to the tertiary chlorides with remarkable ease, the reaction being essentially complete in 2 min at 0°. Since we are doubtless operating in the range where diffusion control must be important, this means that the observed reaction time, 2 min, must represent a maximum, with the actual reaction being considerably faster than that observed.

Representative data are shown graphically in Figure 2. (The interesting behavior of 2-methyl-*endo*-norborneol will be discussed later.)

In a number of cases we compared the relative merits of *n*-pentane, methylene chloride, and carbon tetrachloride as solvents for the reaction. While the results

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(8) To test the utility of the crude chlorides thus prepared, without intermediate purification, for rate measurements, we solvolyzed the products in 80% aqueous ethanol directly and observed the following first-order rate constants measured at 25°: 0.031 hr^{-1} for *t*-butyl chloride, 0.055 hr^{-1} for *t*-amyl chloride, 0.098 hr^{-1} for triethylcarbinyl chloride. Evidently, chlorides prepared in this manner can be utilized directly for rate measurements.

TABLE I

DATA FOR THE HYDROCHLORINATION OF REPRESENTATIVE TERTIARY ALCOHOLS

Alcohol	mmoles	Solvent	Temp, °C	Time,[a] min	Hydrogen chloride used, mmoles	Alkyl chloride obtained, mmoles	Product: $n^{20}D$ or mp, °C	Product: Purity[b] by titrn	Product: Yield isold, %
t-Butyl alcohol	42.1	Neat	Room temp	75	38.3	31		99	74
t-Pentyl alcohol	39.1	Neat	Room temp	15	37.3	38.2	1.4058	100	97
Triethylcarbinol	40.0	Neat	Room temp	7.5	39.9	37.4	1.4330	100	94
Benzhydrol	10.0	CH_2Cl_2	0	2.5	10.3	9.3	1.5957	95	93
Diphenylmethylcarbinol	10.0	CH_2Cl_2	0	3.5	9.5	9.0		(60)[c]	(90)[c]
1-Methylcyclopentanol	18.0	$n\text{-}C_5H_{12}$	10	3.5	17.5	17.5	1.4460	100	96
2-Methyl-*endo*-norborneol	20.1	$n\text{-}C_5H_{12}$	10	26	20.3	17.6	20–25	98	88
1,2-Dimethyl-*endo*-norborneol	20.0	$n\text{-}C_5H_{12}$	0	12	20.3	19.4	120–122	99	97
2-Phenyl-*endo*-norborneol	20.1	$n\text{-}C_5H_{12}$	0	6.5	21.0	18.7	43–45	99	94
	10.0	$n\text{-}C_5H_{12}$	0	1.8[a]	9.9				
	10.0	$n\text{-}C_5H_{12}$	0	2.2[a]	9.6				
	10.0	CH_2Cl_2	0	1.2[d]	10.1				
	10.0	CH_2Cl_2	0	1.0[d]	10.5				

[a] The reaction time is a function of the stirring rate. The values reported should only be considered to be an indication of the very fast rates realized. [b] No detectable vinyl proton and hydroxy group was detected in nmr and infrared spectra. [c] The tertiary chloride is highly unstable and the product appears to lose hydrogen chloride during the aspiration procedure. [d] The data indicate a faster rate in methylene chloride than in *n*-pentane.

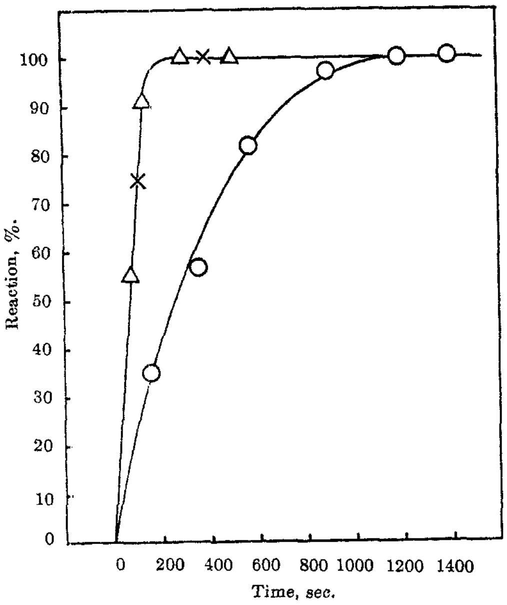

Figure 3.—Rate of absorption of hydrogen chloride by α-methylstyrene at 0°: neat (×), in methylene chloride (2 *M*, △), and in *n*-pentane solution (2 *M*, ○).

hint that methylene chloride is preferable for the hydrochlorination reaction itself, the advantage is very minor. On the other hand, *n*-pentane possesses advantages for the recovery of product by removing the solvent under vacuum, as well as for crystallizing out a solid product at low temperatures. Finally, the use of carbon tetrachloride possesses obvious advantages where it is desired to subject the initial product directly to nmr examination without isolation.

We also explored the effect of temperature. We were able to convert *t*-amyl alcohol to its chloride in a reasonable time at 25, 0, and −45°. Even the secondary alcohol, benzhydrol, absorbed the theoretical quantity of hydrogen chloride in 2.5 min at 0° in methylene chloride solution. Consequently, we tended to carry out our preparations at 0°, except in cases, such as 2-methyl-*endo*-norborneol, where the 0° reaction proved to be relatively slow.

As is shown in Figure 2, all of the compounds absorbed the theoretical amount of hydrogen chloride within 2–3 min, with one exception, 2-methyl-*endo*-norborneol. This alcohol rapidly absorbed 65% of the calculated quantity of hydrogen chloride at 0°, and exhibited no further observable change in the following 10 min. Then a slow further uptake of hydrogen chloride became evident, approaching the theoretical amount over a relatively long period.

Similar behavior was observed at 10°. In this case the second stage was considerably faster, the reaction proceeding to essential completion in 26 min. The initial plateau corresponds closely to the rapid formation of a 1:1 addition compound, which is then transformed only relatively slowly into water, which takes up the additional hydrogen chloride, and the tertiary chloride.

The 1:1 addition compound is probably the oxonium salt, $ROH_2^+Cl^-$. The difference in the behavior of the *exo* and *endo* isomers presumably arises from the same factors which are responsible for the difference in the rates of solvolysis of *exo*- and *endo*-norbornyl derivatives.[9]

Typical data for the hydrochlorination of representative tertiary alcohols are summarized in Table I.

Finally, we examined the hydrochlorination of α-methylstyrene as a representative olefin. At 0° the hydrochlorination proceeded rapidly and quantitatively, being complete in approximately 2 min (Figure 2). At −45° the reaction proceeded equally rapidly. However, at room temperature the addition of hydrogen chloride to the olefin was much slower.[10] Similar negative temperature coefficients for the addition of hydrogen chloride to norbornene[11] and isobutylene[12] have been described.

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(9) For a discussion with pertinent references, see H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Am. Chem. Soc.*, **86**, 1248 (1964).

(10) For the fast reactions we are obviously operating within the rate of diffusion control. Consequently, we cannot conclude from the data at 0 and −45° that the true reaction rates are the same. However, it is safe to conclude from the data that the reaction rate at room temperature is much lower than the rates at 0 and −45°.

(11) L. Schmerling, *J. Am. Chem. Soc.*, **68**, 195 (1946).

(12) F. R. Mayo and J. J. Katz, *ibid.*, **69**, 1339 (1947).

In the hydrochlorination of α-methylstyrene, the use of methylene chloride as a solvent appears to have significant advantages over *n*-pentane in favoring the rate of reaction (Figure 3).

A number of runs was carried out with α-methylstyrene to test the reproducibility of the procedure, as well as to test the effect of solvent on the reaction rate.

Representative data are summarized in Table II.

TABLE II

DATA ON THE HYDROCHLORINATION OF α-METHYLSTYRENE AT 0°

α-Methylstyrene, mmoles	Solvent	Time, sec	Hydrogen chloride used, mmoles	Molar ratio HCl/olefin
40.1[a]	Neat	126	39.2	0.98
10.5	Neat	138	10.9	1.03
10.0	Neat	126	10.1	1.01
9.4	Neat	128	10.0	1.06
9.9	Neat	130	10.0	1.01
9.8	Neat	136	9.6	0.98
10.0	*n*-C_5H_{12}[b]	995	10.1	1.01
10.0	*n*-C_5H_{12}[b]	1100	10.3	1.03
10.0	CH_2Cl_2[b]	61	10.6	1.06
10.0	CH_2Cl_2[b]	123	10.5	1.05
10.0	CH_2Cl_2[b]	120	10.3	1.03

[a] Isolated a 97.5% yield of *t*-cumyl chloride, 99.5% pure by titration, $n^{20}\text{D}$ 1.5230. [b] 2 *M* solution.

Conclusions

It is evident from these results that the automatic hydrogenator previously reported can be readily adapted for the automatic hydrochlorination of reactive alcohols and olefins. This opens up the possibility of reexamining the hydrochlorination of many terpenes and other labile olefins where a knowledge of the structure of the initial reaction product would be of interest. We are currently exploring this possibility. Finally, it appears evident that the general principal appears applicable to many reactions in which one wishes to achieve the automatic, quantitative addition of a gas to a liquid or solid phase.

Experimental Section

Stoichiometry.—The commercial hydrochloric acid utilized was 12.1 *M*. However, hydrogen chloride possesses a modest solubility in sulfuric acid containing several per cent of water. Consequently, it was necessary to establish precisely how much hydrogen chloride would be delivered by the addition of 1.00 ml of the concentrated hydrochloric acid to the sulfuric acid in the generator.

This was done in two ways. One milliliter of water was injected by means of a hypodermic syringe into the reaction flask of the apparatus and the generation of hydrogen chloride was allowed to proceed to completion. The water saturated with hydrogen chloride was titrated, and the value was compared with the number of milliliters of concentrated hydrochloric acid delivered from the buret. Alternatively, successive portions of α-methylstyrene were injected into the reaction flask and the amount of concentrated hydrochloric acid delivered by the buret was noted. Both procedures gave a figure of 11.0 ± 0.1 mmoles of hydrogen chloride generated from each milliliter of the concentrated hydrochloric acid delivered into the generator.

Similarly, by determining the amount of hydrogen chloride required to saturate 1.00 ml of water at 0 and 25°, the figure was arrived at that each mole of tertiary alcohol would require 1.35 moles of hydrogen chloride at 0° and 1.29 moles of hydrogen chloride at 25° to achieve the conversion to the chloride and the saturation of the aqueous phase produced in the reaction. These figures correspond to the values actually observed for the reaction of 2-phenyl-*endo*-norborneol in the apparatus.

Hydrochlorination of 2-Methyl-*endo*-norborneol.—The apparatus was assembled and flushed with hydrogen chloride as is described in the Procedure. The reaction flask was immersed in a bath at 10°, and the reaction was initiated by injecting 20 mmoles (2.53 g) of 2-methyl-*endo*-norborneol in 10 ml of *n*-pentane solution through the injection port. There was an immediate uptake of approximately 75% of the required amount of reagent. Then the reaction proceeded slowly to 100% utilization, being essentially complete in 26 min. The organic layer was withdrawn from the reaction flask and subjected to gentle aspiration to remove dissolved hydrogen chloride. Fresh pentane was added to bring the volume to precisely 10.0 ml, and a 1-ml aliquot was added to 80% aqueous ethanol at room temperature. Standard alkali was added to neutralize the hydrogen chloride produced, the amount corresponding to 97.4% of reactive chloride in solution. This quantity is listed as the purity (titration) in Table I. The remaining solution was evaporated under vacuum to constant weight. There was obtained 2.54 g,[13] 17.5 mmoles, of 2-methyl-*exo*-norbornyl chloride, mp 20–25°.[14] A weighed sample of the chloride was solvolyzed in 80% aqueous ethanol at 25°. There was produced 98.6% of the calculated quantity of hydrogen chloride.

Hydrochlorination of α-Methylstyrene.—In this case the reaction flask was cooled to 0° and the reaction was initiated by injecting 40 mmoles (4.73 g) of α-methylstyrene, $n^{20}\text{D}$ 1.5381. After 10 min, the product was subjected to gentle aspiration to remove dissolved hydrogen chloride. There was obtained 6.02 g (39.2 mmoles) of 2-chloro-2-phenylpropane, $n^{20}\text{D}$ 1.5230. A sample of this chloride was solvolyzed in 80% aqueous ethanol. The hydrogen chloride produced was between 99 and 100% of the theoretical.

Acknowledgment.—This investigation was assisted by Grant 19878 provided by the National Science Foundation.

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(13) Corrected for the aliquot removed in the determination of the yield by titration.

(14) The pure chloride possesses mp 25°: N. J. Toivonen, E. Siltanen, and K. Ojala, *Ann. Acad. Sci. Fennicae, Ser. A II*, 64 (1955).